REMARKS

This Reply is responsive to the Office Action dated October 24, 2000. Reconsideration of the claimed invention in light of the amendments and remarks submitted herein is respectfully requested.

At the outset, Applicants thank the Examiner for granting the interview on April 12, 2001 at which time the rejections of record were discussed. As Applicants understand, the Examiner intends to give careful and complete reconsideration to the amendments and remarks submitted herein, and in the event he decides to maintain the pending rejections, he will request that Supervisor Chan and Group Director Doll also give careful and complete consideration to the pending rejections prior to issuing a final action. Should Supervisor Chan and Group Director Doll be included in reviewing this file, Applicants emphasize that the main point of contention is the Examiner's overly stringent application of the written description requirement of §112, first paragraph. Indeed, Applicants respectfully submit that the written description standard applied by the Examiner to date is wholly improper as it conflicts to established case law.

In particular, Applicants request that Supervisor Chan and Group Director Doll independently re-evaluate the Examiner's assertion that a combined therapeutic regimen involving a generic chimeric anti-CD20 antibody fails to find support in the parent application because the specific example provided refers only to the exemplary antibody. The Examiner maintains this rejection despite the fact that it is clear from a reading of the parent specification as a whole that applicants intended the invention to encompass chimeric anti-CD20 antibodies in general and not solely the exemplified antibody (e.g., see page 12, line 26, page 13, line 5, and numerous other places in the specification that refer to chimeric anti-CD20 antibodies generically, and not with reference to C2B8). The standard repeatedly applied by the Examiner requires *ipsis verbis* support for subject matter which any person skilled in the art reading a specification could see was in the Applicants' possession. This unusually stringent standard for §112, written description, is not only at issue in this case, but in every related case in front of Examiner Schwadron. Applicants submit these grounds of rejection constitute an improper impediment to obtaining the scope of protection to which they are entitled based on the application as filed. Favorable resolution of this issue by the Office is respectfully requested.

This issue has become particularly important given that Applicants' competitors are obtaining broad patents, whereas Applicants can only obtain allowance of very narrow patent claims when faced with Examiner Scwadron's ipsis verbis standard of written description. For instance, Applicants' competitor Kaminski et al recently obtained a broad patent, U.S. Patent 6,090,365, having a priority date of September 16, 1993, which contains the following claim:

> 11. A method of lymphoma therapy which comprises:
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> performing a first treatment wherein an unlabelled antibody or antibody fragment that binds to the CD20 antigen present on lymphoma cells is administered to a patient; and
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> performing on the patient a second treatment selected from the group consisting of administering external beam radiation, administering a radioisotope conjugated to an antibody or antibody fragment that binds to an antigen on B cells other than CD20, and administering a chemotherapeutic agent,
>
> wherein the first and second treatments are performed in any order or concurrently.

Examiner Schwadron is aware of this patent, and aside from commenting that he would not have allowed such claims and that he has no control over other Examiners, he has not indicated that he will even assist the Applicants to obtain allowable claims such that an interference can be provoked. Applicants believe this course of action by the PTO to be improper and strongly urge an expedited review in this matter by appropriate personnel.

Even if the Examiner agrees to allow Applicants to copy claims so as to provoke an interference, i.e., in a continuation application, the fact that the pending rejections continue to be maintained in this application is an obvious inconsistency that potential infringers could use to their benefit, particularly in view of the *en banc* Festo decision recently issued by the Federal Circuit. Applicants believe that the parent specification clearly conveys that Applicants were in possession of the generically claimed invention despite the arguable lack of *ipsis verbis* support, and that Applicants would prevail in an interference between the

issued Kaminski patent. Note that the priority dates of the Kaminski patent and the present application are less than three months apart.

Once again, it is imperative that the ongoing disagreement between Applicants and the Examiner as to the appropriate standard for a written description rejection be resolved by the Office immediately so that Applicants are not put at a disadvantage with respect to their competitors in the marketplace. Accordingly, should the Examiner maintain the rejections, Applicants respectfully request that Supervisor Chan and Group Director Doll review the present case and communicate as to whether they support the same stringent standard. While other avenues are available for resolving this question, they are extremely lengthy and may cause irreparable harm to the Applicant as they are precluded from taking appropriate actions against potentially infringing competitors. However, in the interim, Applicants will lose years in the marketplace to an undeserving competitor, a harm that will not be vindicated given the length of the appeals process.

Turning now to the Office Action, Claim 12 is amended above to maintain antecedent basis with claim 11, on which it is dependent. No new matter has been added.

New claims 16-20 have been added which are based on pending claims 11-15, except the claims specify that the antibody employed in the recited method achieves the recited results over the entire claimed dosage range. These claims find support in claims 11-15, and at pages 15-16 in the specification where the optimal effective dosage range of the subject antibody is disclosed. No new matter has been added.

Applicant acknowledges that a new oath or declaration is still required and again asks that this requirement be held in abeyance until the indication of allowance.

The title of the application as filed was objected to, so a new title is submitted above which replaces the original title. Withdrawal of this objection is respectfully requested.

Claims 11-15 were objected under 35 U.S.C. § 112, first paragraph, for allegedly failing to find written description in the application as filed. Specifically, the Examiner alleges that there is no support for the claimed dosage of "about 0.4 mg/kb" because the specification discloses a range of dosages from about 0.4 to about 20 mg/kg. Accordingly, the Examiner asserts that an upper range is required.

Applicants respectfully submit that the Examiner appears to be confusing the situation with that encountered by the Applicants in In re Wertheim, 541 F.2d 547 (CCPA 1976). The

applicants there attempted to submit a claim with a limitation reading "at least 35%" when the priority application disclosed a range of 25 to 60%. The Examiner rejected the claim in that case as including doses that were above the upper limit of the range disclosed in the priority application. Applicants have enclosed a copy of In re Wertheim for the Examiner's convenience.

Here, the issue is clearly different. Applicants are not reciting "*at least*" about .4 mg/kg in attempt to broaden the upper limit of the acceptable range of dosages disclosed. Rather, Applicants are merely limiting the claims to the lower end of the dosage by reciting a particular dosage that finds explicit support in the application as filed. Indeed, Wertheim addresses a similar instance in the same case where, although a claim containing the limitation "at least 35%" was rejected, a claim containing a narrower range within the broader range was said to be supported by the priority application even though not present ipsis verbis. As the Wertheim court stated:

> The PTO has done nothing more than to argue lack of literal support, which is not enough. If lack of literal support alone were enough to support a rejection under §112, then the statement of In re Lukach [citations omitted] that "the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of §112," is empty verbiage.

Here, the present claims are certainly supported by the disclosure according to the test set forth in Wertheim because the claimed limitation of "about 0.4 mg/kg" finds *ipsis verbis* support in the application as filed.

As an alternative, Applicants have also submitted new claims 16-20 to emphasize that an antibody that is used in the methods of the invention will have the claimed functional activity across the entire range claimed if the Examiner continues to insist in an upper limit in the claims. However, Applicants respectfully submit that such a requirement is not in accordance with the case law. Therefore, the rejection should be withdrawn.

Next, claim 12 was rejected under 35 U.S.C. §112, second paragraph because the claimed dosage range does not find antecedent basis in claim 11 as amended. Claim 12 has been amended to correct this oversight, thus, the rejection is now moot.

The Examiner makes several observations about priority for the claimed invention. Apparently, the Examiner believes that there is no support for claims 11-13 in the priority

application because, first, the priority application only discloses the combined use of the specific anti-CD20 antibody C2B8 in combination with a chemotherapeutic agent, not the general class of chimeric anti-CD20 antibodies as claimed. And second, the Examiner further asserts that there is not disclosure of "at least one chemotherapeutic agent" because only one ("a") agent is disclosed in the priority application as being used with C2B8 and the reference incorporated by reference therein refers to the use of individual chemotherapeutic agents, not mixtures.

Applicants respectfully submit that a prior disclosure of a species enables a genus but not vice versa. Thus, it appears that the Examiner has confused the rules regarding priority of invention. Indeed, a prior disclosure of a broad genus should not be seen as enabling a specific embodiment, in order to allow future practitioners to develop particular species having potential new characteristics. However, it would make no sense to assert that a prior disclosure of a specific species does not provide priority for the broader genus, particularly when the priority application discloses that particular product in a generic way (see page 9, Summary of Invention). Indeed, according to MPEP 201.11 (When not entitled to priority...), the test appears to be whether a particular "feature" was disclosed generically, not whether a particular claim finds *ipsis verbis* support. Here, Applicant's priority application discloses the particular feature of a genus of chimeric anti-CD20 antibodies in treatment methods for B cell lymphoma, and also discloses combination methods using an exemplary antibody in combination with chemotherapeutic agents. Thus, priority exists in the parent application.

Regarding the feature "at least one chemotherapeutic agent," Applicants respectfully submit that one of skill in the art in reading the list of agents on page 62 of the priority application – cyclophosphamide, doxorubicin, vincristine and prednisone – would have immediately known that combinations of chemotherapeutic agents could be employed, given that the specific agents listed were known in the art at the time as the combination regimen "CHOP." In fact, chemotherapeutic agents were commonly employed as part of multi-agent regimens and were rarely used individually. Applicants have attached nine abstracts of references available as of the priority date of the invention that prove not only that the four agents listed by name in the priority application were part of a known chemotherapeutic combination regimen, but also that other combination regimens were commonly employed by those of skill in the art. Given this evidence reflecting what would have been common

knowledge at the time, Applicants respectfully request that priority in the parent application for the instant claims be confirmed.

Applicants respectfully request that the rejection under §102(e) based on Anderson continue to be held in abeyance pending submission of the requisite declaration.

Claim 11 remains rejected under §102(e)/103(a) based on Kaminski et al. Essentially, the Examiner believes that because Kaminski discloses a prophetic chimeric anti-CD20 antibody at column 7, that such an antibody would necessarily have the apoptotic activity of the antibody as employed in the present claims. However, Applicants respectfully note that the motivation in Kaminski is only to avoid a HAMA reaction, not to optimize functions relating to the Fc region of the antibody. Therefore, one would not be motivated in view of Kaminski alone to design an antibody that has the functional characteristics of the chimeric antibody disclosed in the present application.

Furthermore, as discussed in the declaration by Darrell Anderson signed November 7, 1996 and submitted previously in this case, it would be highly unreasonable to expect that other anti-CD20 antibodies would inherently show equivalent behavior as the subject antibody given the extraordinary level of depletion achieved at such low doses. Indeed, as stated by Dr. Anderson, the subject antibody possesses "unparalleled" and "extensive" depletion of B cells uncommon to other chimeric constructs tested (see pages 4-5 of the Declaration). Hence, given such unexpected results, one would not have expected the mere substitution of the constant region to achieve the claimed functional effects, particularly with no direction in the Kaminski specification to seek such results. Contrary to what the Examiner seems to imply, such activity is not inherent in the design of any chimeric anti-CD20 antibody absent specific motivation to achieve such activity.

Of course, given the knowledge of the present invention and the fact that such a level of activity is possible, those of skill in the art could screen for chimeric anti-CD20 antibodies having the level of activity exemplified by the subject antibody and recited in the present claims. However, without such knowledge in hand, such an achievement would have been truly unexpected. Reconsideration and withdrawal of this rejection is respectfully requested.

Finally, claims 11-13 remain rejected under §103(a) as being unpatentable over Press et al., in view of Hellstrom and Robinson. In maintaining the rejection, the Examiner asserts that the disclosed dosage employed in Press et al. (10 mg/kg) is within the claimed dosage of

about .4 mg/kg. Applicants respectfully submit that it is quite a reach to say that the dosage of 10 mg/kg employed in Press et al. would be taken by those of skill in the art as being coextensive with "about .4 mg/kg," particularly when Press et al. discloses that relatively high doses need to be employed to achieve relatively transient results as compared to those observed in the present invention. Indeed, it appears that 10 mg/kg, if overlapping at all with the range employed in the instant application (which again is quite a stretch), is at the low end of the range used in Press et al., who actually recommends dosages of 1 and even 2g as optimal (see the Blood citation). Therefore, those of skill upon reading the cited art would certainly be directed away from the claimed dosage of about .4 mg/kg rather than towards it. "A prima facie case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention." In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). See MPEP 2144.05.

Thus, given that the relatively high dosage range of Press et al. cannot be taken as rendering obvious the unexpectedly low doses employed in the present invention, and particularly do not fall anywhere close to a dose of about 0.4 mg/kg given that the lowest dose employed is 10 mg/kg and Press (Blood) actually recommends much higher doses of 52 mg/kg to 2 g, the cited references do not render obvious the claimed invention. The other references cited do not make up for the deficiency in Press failing to teach or render obvious the dosages of chimeric anti-CD20 antibody employed. Given that such B cell depleting activity at such low doses is truly unexpected as discussed above in light of Kaminski, this rejection under §103(a) should now be withdrawn.

This Reply is fully responsive to the Office Action dated October 24, 2000. If the Examiner would like to discuss any further issues relating to the subject application, or if he has any further comments or questions regarding the pending rejections or the Reply above, he is encouraged to contact the undersigned so that prosecution can be expedited.

In view of the foregoing, the application is now believed to be in form for allowance, and such action is hereby solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____
Bonnie D. Weiss
Reg. No. 43,255

1100 New York Avenue, NW
Ninth Floor
Washington, DC 20005-3918
(202) 861-3000
(202) 822-0944 Facsimile

Attorney Matter No. 037003-0275463
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Enclosure: Appendix

APPENDIX: VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Title:

Delete the present title of "Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma" and insert the following new title, --COMBINED THERAPY OF B CELL LYMPHOMA WITH ANTI-CD20 ANTIBODY AND CHEMOTHERAPEUTIC AGENTS--.

In the Claims:

12. (Amended) The method of Claim 11, wherein said chimeric anti-CD20 antibody is administered once a week at [a] said dosage [ranging from 0.4 to about 20 mg/kg body weight] for about 2 to 10 weeks.